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ORIGINAL ARTICLE

Factors associated with trial recruitment, preferences, and treatments received were elucidated in a comprehensive cohort study

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Abstract

Objectives: Recruitment to pragmatic trials is often difficult, and little is known about factors associated with key participation and treatment decisions. These were explored in the Prostate cancer testing and Treatment (ProtecT) study.

Study Design and Setting: Baseline sociodemographic, patient-reported outcome, clinical history, and prostate cancer biopsy data were collected for all patients eligible to take part in the ProtecT trial, in a comprehensive cohort design. Men who rejected randomization specified a preferred option and were followed up identically to the randomized cohort. Factors associated with participation decisions, patient preferences, and reasons for changing treatment were explored.

Results: Of 2,664 men with clinically localized prostate cancer, 997 (37%) rejected randomization. Their treatment preferences and subsequent treatment choices/changes in both randomized and treatment choice cohorts were strongly associated with prostate cancer risk features: toward active monitoring for low-risk disease and toward radical options with higher risk prostate cancer. Among many factors measured, only a small number of weak associations were found for occupation groups and some patient symptoms. Similar percentages changed from the random allocation and initially stated preference.

Conclusion: The comprehensive cohort design provided new insights into trial recruitment and participation decisions. Opportunities to improve recruitment by supporting recruiters with equipoise and patient preferences were identified.

Keywords: Randomization; Preferences; Randomized trial; Recruitment; Comprehensive cohort; Research participation

1. Introduction

Randomized controlled trials (RCTs) are the design of choice for evaluating the effectiveness of health-related interventions because the process of randomization aims to remove most of the biases that occur when clinicians recommend, or patients choose, specific treatment options. However, it is common for pragmatic RCTs to experience difficulties with recruitment, particularly when interventions are very different, for example, where treatment options can be invasive, or unavailable in routine practice, or involve a nonactive or monitoring strategy. RCT recruitment should only occur when clinicians are sufficiently uncertain (in ‘‘equipoise’’) about the optimal intervention for a patient [1] and when patients have received clear information that ensures they do not have strong preferences for a particular option and can provide fully informed consent to take part [2]. Equipoise and patient preferences are examples of ‘‘hidden challenges’’ to recruitment that are difficult to elicit and measure [3]. Achieving equipoise in relation to an individual patient remains difficult for clinicians, particularly if there is a conflict with their own beliefs about

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What is new?

Key findings

- In a comprehensive cohort study including all patients eligible for the Prostate testing for cancer and Treatment trial, 1,643 (62%) agreed to be randomized, and 997 men (37%) rejected randomization and were followed up as a ''treatment choice'' cohort. Treatment preferences, changes of treatment, and treatments received in the randomized and treatment choice cohorts were strongly associated with prostate cancer risk features, with few other associations.
- Percentages subsequently changing treatment from the random allocation or initially stated preference were very similar.

What this adds to what was known?

- This article contributes new insights that increase our understanding of the role played by patient preferences and clinician equipoise during recruitment to pragmatic randomized controlled trials (RCTs). It also identifies opportunities to address some of the challenges to recruitment.

What is the implication and what should change now?

- Interventions need to be developed or extended to support recruiters with expressing equipoise and understanding patient preferences.
- Comprehensive cohort studies could be undertaken more often to investigate and address RCT recruitment issues, particularly in areas of high public health importance.

interventions and perceptions of risks they believe apply to specific patients [4,5]. Strong patient preferences are also frequently cited as a common and major barrier to RCT recruitment [6–8], with concerns that the absence of large numbers of patients who are eligible for an RCT but not recruited will likely limit an RCT's generalizability [9].

RCT designs that could enable the exploration of the influences of these issues include ''comprehensive cohorts,'' where patients are offered randomization, but those with strong preferences can choose a treatment instead, with all followed-up [10], or ''preference'' trials, where patients are asked to report their preferences before or after they have been randomized [11]. These designs are usually considered a pragmatic approach when recruitment is difficult, and they have provided useful information about the acceptability of options [12], rare or important outcomes [13], and generalizability [14]. They are uncommon because of resource constraints and difficulties analyzing small randomized groups [15]. These designs provide opportunities to investigate recruitment decision-making and selection biases between randomized and preference groups, but these issues have been little considered in the previously mentioned studies. Overall, very little is known about these crucial aspects of the recruitment process in RCTs. We were able to investigate these issues in the Prostate testing for cancer and Treatment (ProtecT) comprehensive cohort study and embedded RCT.

The ProtecT RCT compared three very different treatments for clinically localized prostate cancer: active monitoring (a surveillance strategy), surgery (radical prostatectomy), or radiotherapy (conformal external beam with neoadjuvant androgen deprivation therapy). The design of the ProtecT treatment RCT and baseline findings of the randomized participants were reported in 2016 [16]. ProtecT RCT participants were recruited during a program of population-based prostate-specific antigen (PSA) testing [17]. Follow-up was undertaken within a comprehensive cohort study design including all men diagnosed with prostate cancer: those eligible for the RCT who either agreed to be randomized or chose their treatment and those found to be ineligible because of advanced prostate cancer or comorbidities. The design of the ProtecT comprehensive cohort study, representativeness of the PSA-tested cohort, and generalizability of the follow-up patient groups were reported in 2018 [17].

The present study focuses on the recruitment and RCT participation decisions of 1,643 patients who agreed to be randomized in the ProtecT treatment RCT (''randomized'' cohort) and 997 who declined randomization and chose their treatment (''treatment choice'' cohort). The aim of the analysis was to understand RCT recruitment and selection issues associated with the expression of treatment preferences, RCT participation, changes of management after randomization or treatment choice, and final receipt of primary treatment; assessed in the randomized and treatment choice cohorts in the ProtecT comprehensive cohort study.

2. Methods

2.1. Study design and data collection

The design and recruitment methods of the ProtecT trial have been published previously [16,17] and are described in brief previously. As indicated, a program of population-based PSA testing of more than 110,000 men aged 50 to 69 years in the United Kingdom between June 1999 and January 2009 led to the detection of prostate cancer in 3,221 men, of whom 2,664 (83%) were eligible to participate in the ProtecT treatment RCT comparing active monitoring, surgery, or radiotherapy. The cancer diagnosis was given by a consultant urologist who provided basic information about the RCT and an information sheet. Patients

returned for a longer appointment with a trained nurse who explained the details of the RCT and explored men's treatment preferences to ensure they reached an informed decision about whether or not to participate in the RCT. If men agreed to be randomized, they were informed about the allocation; if they declined to be randomized, they were asked to specify their preferred option.

At the time of PSA testing, participants provided sociodemographic and clinical history information and completed a brief questionnaire containing generic and condition-specific patient-reported outcome measures (PROMs). They completed more detailed PROMs at the prostate biopsy appointment, and clinicopathologic information from biopsies was also recorded. Primary treatment received was defined as the treatment starting/occurring within 12 months of diagnosis (with at least two PSA tests needed for receipt of active monitoring, and radiotherapy was received if completed within 15 months) to ensure parity between the randomized and ''treatment choice'' cohorts. The only other major treatment received was brachytherapy (this had different inclusion criteria). Any other treatment, no treatment, or treatments received outside the specified time window were categorized as ''other.''

Approval for the study was obtained from the UK East Midlands (formerly Trent) Multicenter Research Ethics Committee (01/4/025).

2.2. Statistical methods

Associations between baseline sociodemographic, clinical and PROMs data, clinicopathologic findings from biopsy specimens, and the following were explored:

1. Consent to randomization or stating a treatment preference
2. Changing from the random allocation or stated preference in randomized and treatment choice cohorts:
   (a) to a more radical option (from active monitoring to surgery or radiotherapy/brachytherapy) or
   (b) to a less radical option (from surgery or radiotherapy/brachytherapy to active monitoring)
3. Primary treatment received in randomized and treatment choice cohorts (later changes of management will be reported in future articles)

For (skewed) continuous sociodemographic outcomes, medians and interquartile ranges were reported; continuous outcomes from questionnaire data were presented with means and standard deviations to identify ceiling effects. Kruskal−Wallis tests were used to compare continuous baseline characteristics across groups defined by treatment received. For categorical outcomes, such as previous PSA test, treatment received groups were compared using logistic regression, followed by a postestimation Wald test to compare the treatment groups or cohorts simultaneously [17]. Ordered categorical outcomes such as occupation and cancer staging were analyzed using ordinal logistic regression followed by a Wald test with the most desirable/least worst category as the base comparator/reference group. PROMs were: generic health status (SF-12 [18]), Hospital Anxiety and Depression scale ([19]), urinary symptoms (ICSmaleSF [20] and Expanded Prostate Cancer Index Composite [EPIC] urinary domain [21]), urinary incontinence (ICIQ [22]), and sexual and bowel dysfunction (EPIC [21]). These were analyzed as specified by their developers; categorical outcomes were dichotomized as ''never'' versus ''ever.'' Differences between the randomized and treatment choice cohorts were compared using Mann−Whitney tests and logistic regression and ordinal regression models.

Given the exploratory nature of the study and large number of tests, greater attention was given to descriptive statistics where the magnitude of effects was substantial, rather than just relying on P values. Differences considered to be of clinical importance (0.5 standard deviations or 10%) were also considered when evaluating the relationship between baseline factors and treatment preferences and changes. All statistical analyses were conducted using STATA version 15.1 (StataCorp LLC, College Station, TX).

3. Results

Of the 2,664 men diagnosed with clinically localized prostate cancer who were eligible for the three-arm ProtecT trial (24 randomized in a discontinued two-arm version were excluded), 997 (37%) declined randomization (Fig. 1 shows participant flow in the randomized and treatment choice cohorts).

3.1. Randomized cohort

Overall, 1,273 (78%) of the 1,643 randomized participants received the random allocation as their primary treatment (including brachytherapy as a form of radiotherapy). More accepted the random allocation to active monitoring 457 (84%, 95% confidence interval [CI] 81−87) than to surgery 397 (72%, 95% CI 68−76) or radiotherapy 419 (77%, 95% CI 73−80; Fig. 1). Most of those who did not accept the random allocation opted for one of the three RCT treatments (Table 1). Most switching from an allocation to radical treatment (surgery or radiotherapy) opted for active monitoring, with smaller numbers changing to an alternative radical option. Those changing from the active monitoring allocation were twice as likely to opt for surgery (n = 49) as radiotherapy (n = 25).

There was strong evidence that changing to a radical option was associated with having higher risk disease features (including a higher PSA, higher cancer grade or stage, and having a larger cancer with more positive cores at biopsy) and changing to active monitoring was associated with lower risk disease and not being married (Table 2).

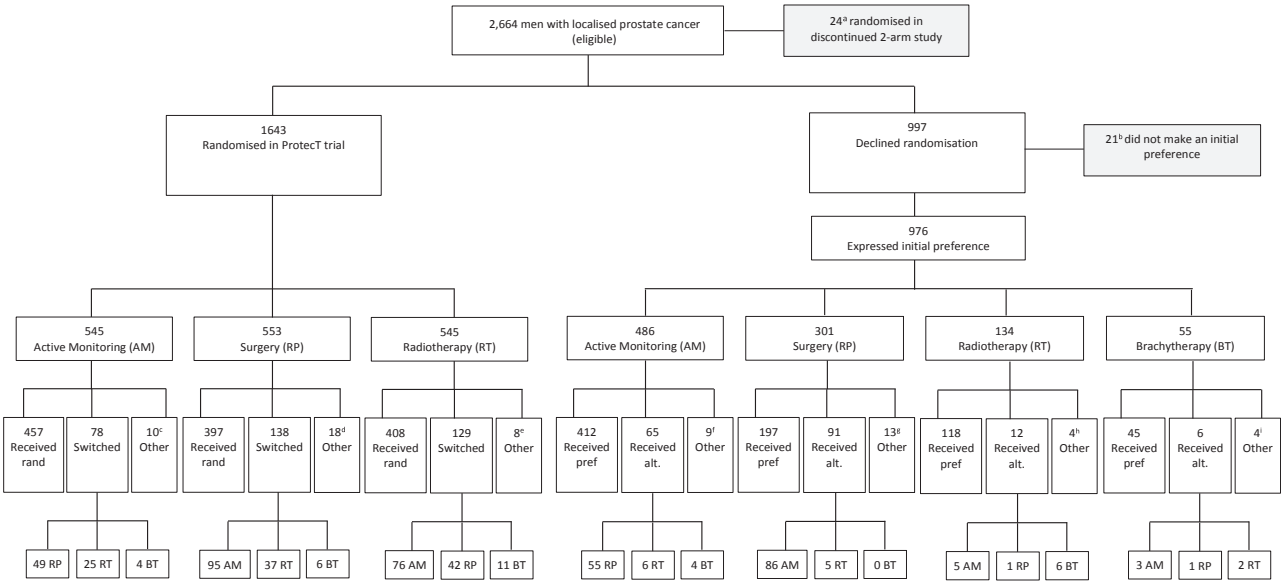

Fig. 1. Treatment preference and random allocation decisions in the ProtecT trial comprehensive cohort. [a] Excluded. [b] 8 received surgery, 1 AM, 2 radiotherapy, 1 brachytherapy, 6 withdrew, 2 other, 1 died before commencing treatment. [c] 6 received treatment outside time window, 1 another treatment, 2 withdrew and 1 died before commencing treatment. [d] 13 received treatment outside time window, 3 another treatment and 2 withdrew. [e] 7 received treatment outside time window and 1 withdrew. [f] 4 received treatment outside time window, 1 another treatment and 4 withdrew. [g] 3 received treatment outside time window, 8 another treatment and 2 withdrew. [h] 3 received treatment outside time window and 1 another treatment. [i] 1 received treatment outside time window, 1 another treatment and 2 withdrew.

There was weak evidence that those in managerial/professional occupations were more likely to switch in either direction than other occupational groups, and that lower levels of anxiety and depression were seen among those who changed. Weak evidence suggested that men with urinary symptoms that bothered them were more likely to switch to a radical treatment and those with more bowel and sexual dysfunction to switch to active monitoring (Table A2).

3.2. Treatment choice cohort

Of the 997 men who declined randomization, almost all (976) indicated a treatment option they preferred instead (Fig. 1). They divided into 486 (50%) stating a preference for active monitoring, and the remainder a radical option, most opting for surgery 301 (31%), only 134 (14%) radiotherapy, and 55 (6%) brachytherapy (Table 1). Overall, 780

Table 1. Treatment received compared with random allocation or initially expressed preference, showing numbers switching or changing management

Treatment allocation or preference	Primary treatment received				
	Active monitoring, *n* (%)	Radical prostatectomy, *n* (%)	Radiotherapy, *n* (%)	Brachytherapy, *n* (%)	Other, *n* (%)
Random allocation					
Active monitoring	**457 (84)**	49 (9)	25 (5)	4 (1)	10 (2)[a]
Radical prostatectomy	95 (17)	**397 (72)**	37 (7)	6 (1)	18 (3)[b]
Radiotherapy	76 (14)	42 (8)	**408 (75)**	11 (2)	8 (1)[c]
Initially expressed preference					
Active monitoring	**412 (86)**	55 (11)	6 (1)	4 (1)	9 (2)[d]
Radical prostatectomy	86 (29)	**197 (65)**	5 (2)	0 (0)	13 (4)[e]
Radiotherapy	5 (4)	1 (1)	**118 (88)**	6 (4)	4 (3)[f]
Brachytherapy	3 (5)	1 (2)	2 (4)	**45 (82)**	4 (7)[g]
Other/none	1 (5)	8 (38)	2 (10)	1 (5)	9 (43)

Bold face shows where the allocation or preference was the primary treatment received.
[a] 6 outside time window, 1 another treatment, 2 withdrew, and 1 died before commencing treatment.
[b] 13 outside time window, 3 another treatment, and 2 withdrew.
[c] 7 outside time window and 1 withdrew.
[d] 4 outside time window, 1 another treatment, and 4 withdrew.
[e] 3 outside time window, 8 another treatment, and 2 withdrew.
[f] 3 outside time window and 1 another treatment.
[g] 1 outside time window, 1 another treatment, and 2 withdrew.

Table 2. Baseline sociodemographic and clinical factors for those who agreed to be randomized and then received the random allocation or switched to active monitoring or a radical option

Baseline factor	Switched to radical treatment[a] (*n* = 78)	Switched to active monitoring[b] (*n* = 171)	Received random allocation (*n* = 1,273)
Age	*n* = 78	*n* = 171	*n* = 1,273
Median age (IQR)	60.0 (57.0, 64.0)	63.0 (58.0, 66.0)	62.0 (58.0, 66.0)
P value	*P* = 0.016		
Ethnicity			
White, *n* (%)	76 (97)	166 (97)	1,247 (99)
Other, *n* (%)	2 (3)	5 (3)	11 (1)
P value	*P* = 0.051		
Marital status			
Married/living as married, *n* (%)	68 (87)	128 (75)	1,079 (85)
Other (e.g., divorced), *n* (%)	10 (13)	43 (25)	183 (15)
P value	*P* = 0.001		
Occupation (present or last paid)			
Managerial, *n* (%)	40 (52)	77 (45)	517 (41)
Intermediate, *n* (%)	8 (10)	30 (18)	199 (16)
Working, *n* (%)	29 (38)	63 (37)	539 (43)
P value	*P* = 0.154		
Cancer/treatment history			
Previous PSA test, *n* (%)	12 (16)	22 (13)	172 (14)
P value	*P* = 0.864		
Previous urinary/prostate treatment, *n* (%)	3 (4)	15 (9)	114 (9)
P value	*P* = 0.311		
Family history of cancer (prostate only), *n* (%)	7 (10)	10 (7)	91 (8)
P value	*P* = 0.709		
Family history of cancer (all), *n* (%)	42 (55)	79 (50)	719 (60)
P value	*P* = 0.047		
Deprivation score	*n* = 76	*n* = 170	*n* = 1,259
Living in an area of deprivation, *n* (%)	8 (11)	20 (12)	196 (16)
P value	*P* = 0.237		
PSA level (minimum *n*)	*n* = 78	*n* = 169	*n* = 1,263
Median baseline PSA level (IQR)	6.1 (4.1, 8.5)	4.4 (3.5, 6.6)	4.6 (3.6, 6.5)
P value	*P* < 0.001		
Median biopsy PSA level (IQR)	6.3 (4.0, 9.3)	4.5 (3.5, 6.6)	4.7 (3.6, 6.8)
P value	*P* < 0.001		
Gleason (aggressiveness) score, *n* (%)			
6	53 (68)	145 (85)	977 (77)
7	20 (27)	24 (14)	271 (21)
8–10	5 (6)	2 (1)	25 (2)
P value	*P* = 0.006		
Cancer staging, *n* (%)			
T1	54 (69)	142 (83)	965 (76)
T2	24 (31)	29 (17)	308 (24)
P value	*P* = 0.038		
Cancer risk[c], *n* (%)			
Low	31 (40)	117 (68)	737 (58)
Intermediate	42 (54)	52 (30)	511 (40)
High	5 (6)	2 (1)	25 (2)
P value	*P* < 0.001		

(*Continued*)

Table 2. Continued

Baseline factor	Switched to radical treatment[a] (n = 78)	Switched to active monitoring[b] (n = 171)	Received random allocation (n = 1,273)
Biopsy cores invaded with cancer, *n* (%)			
1	17 (22)	58 (34)	410 (33)
2	17 (22)	48 (28)	248 (20)
3+	44 (56)	63 (37)	601 (48)
P value	$P = 0.028$		
Perineural invasion			
No (%)	59 (76)	145 (85)	1,002 (80)
Yes (%)	19 (24)	25 (15)	249 (20)
P value	$P = 0.154$		
Length of tumors (minimum *n*)	$n = 72$	$n = 150$	$n = 1,157$
Medium maximum length (mm) in any one core (IQR)	4.0 (2.0, 6.0)	2.0 (1.0, 4.0)	3.0 (1.0, 6.0)
P value	$P < 0.001$		
Median aggregate length (mm) of tumors (IQR)	6.5 (2.0, 13.0)	3.0 (1.0, 6.5)	4.0 (2.0, 11.0)
P value	$P < 0.001$		

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen.

P values are three-way comparisons, using a logistic or ordinal logistic model followed by a Wald test for categorical outcomes and a Kruskal–Wallis test for continuous outcomes.

[a] Moving from an initial preference of active monitoring to receiving radical prostatectomy, radiotherapy, or brachytherapy.

[b] Moving from an initial preference of radical prostatectomy, radiotherapy, or brachytherapy to receiving active monitoring.

[c] Risk was defined as "Low" if T1 and G $\leq$ 6 and pccPSA $<$ 10, "High" if G $\geq$ 8, and "Intermediate" for all other combinations of stage, grade, and PSA.

(80%) went on to receive the treatment they initially expressed a preference for (combining radiotherapy and brachytherapy)—a similar percentage as the 78% who received their random allocation (as mentioned earlier). High percentages of those indicating a preference for active monitoring (85%, 95% CI 82–88), radiotherapy (93%, 95% CI 88–97), or brachytherapy (85%, 95% CI 76–95) went on to receive that option (82%–88%), whereas a much smaller percentage went on to receive their initial preference for surgery (65%). The relatively small numbers who changed from a preference for active monitoring, radiotherapy, or brachytherapy received similar options to those switching from the random allocation, whereas the majority of those who changed from an initial preference for surgery received active monitoring (86/104).

There was weak evidence that those with managerial occupations were more likely to change from their initial preference (in either direction) compared with those in other occupations. There was stronger evidence that changing from their preference was associated with clinical factors relating to their cancer—with those moving to radical options having higher risk disease, whereas those moving to active monitoring tended to have lower risk cancer features (Table 3). There was no evidence that anxiety or depression or sexual or bowel symptoms were associated with changing, although lower levels of urinary symptoms interfering with life were associated with changing to active monitoring (Table A3).

3.3. Factors associated with primary treatment received

There was some evidence of movement toward surgery/radiotherapy for those with higher risk cancer and toward active monitoring for those with lower risk disease in relation to treatments received in the randomized cohort (Table 4 and Table A4). Those opting for brachytherapy were a small (n = 21) and a highly selected group of younger men mostly with professional/managerial occupations and lower risk disease (reflecting the narrower eligibility criteria for this treatment).

The treatment choice cohort groups were not as well balanced in numbers or baseline factors as the randomized [16]: 507 (52%) received active monitoring, 262 (27%) surgery, 133 (13%) radiotherapy, 56 (6%) brachytherapy, and 39 "others" (11 received treatment outside the time window, 14 withdrew, 1 died, and 13 received another treatment; Fig. 1). There was evidence that occupation type and cancer risk features were associated with the receipt of particular primary treatment options (Table 5). Men who received active monitoring had the least severe disease features, whereas those who received surgery or radiotherapy were more likely to have higher risk disease with more adverse features at biopsy. Those receiving brachytherapy were more likely to have had a PSA test previously (29%), have the lowest risk disease, and to be in managerial/professional occupations (80%), contrasting particularly with only 36% who received radiotherapy. There was little evidence of associations between PROMs and

Table 3. Baseline sociodemographic and clinical factors of those who declined randomization and expressed an initial preference and then either received their original preference or changed to another option

Baseline factor	Changed to a radical treatment[a] ($n = 65$)	Changed to active monitoring[b] ($n = 94$)	Received original preference ($n = 780$)
Age	$n = 65$	$n = 94$	$n = 780$
Median age (IQR)	62.0 (57.0, 65.0)	62.0 (58.0, 65.0)	62.0 (58.0, 65.0)
P value	$P = 0.862$		
Ethnicity			
White, *n* (%)	63 (98)	93 (99)	771 (99)
Other, *n* (%)	1 (2)	1 (1)	6 (1)
P value	$P = 0.790$		
Marital status			
Married/living as married, *n* (%)	52 (81)	76 (81)	661 (85)
Other (e.g., divorced), *n* (%)	12 (19)	18 (19)	115 (15)
P value	$P = 0.420$		
Occupation (present or last paid)			
Managerial, *n* (%)	40 (63)	55 (61)	382 (50)
Intermediate, *n* (%)	8 (13)	12 (13)	126 (16)
Working, *n* (%)	16 (25)	23 (26)	260 (34)
P value	$P = 0.030$		
Cancer/treatment history, *n* (%)			
Previous PSA test	9 (14)	14 (15)	140 (18)
P value	$P = 0.604$		
Previous urinary/prostate treatment	4 (6)	7 (8)	64 (8)
P value	$P = 0.850$		
Family history of cancer (prostate only)	7 (13)	8 (10)	64 (9)
P value	$P = 0.710$		
Family history of cancer (all)	36 (59)	50 (57)	430 (59)
P value	$P = 0.939$		
Deprivation score (*n*)	$n = 63$	$n = 92$	$n = 765$
Living in an area of deprivation, *n* (%)	7 (11)	12 (13)	87 (11)
P value	$P = 0.889$		
PSA level (minimum *n*)	$n = 52$	$n = 82$	$n = 697$
Median baseline PSA level (IQR)	5.6 (3.7, 7.7)		
P value	$P = 0.093$		
Median biopsy PSA level (IQR)	6.0 (4.1, 8.1)	4.6 (3.6, 5.8)	4.7 (3.6, 6.8)
P value	$P = 0.211$	4.8 (3.8, 6.2)	4.7 (3.6, 6.9)
Gleason score, *n* (%)			
6	45 (70)	81 (86)	585 (75)
7	17 (27)	12 (23)	179 (23)
8–10	2 (3)	1 (1)	15 (2)
P value	$P = 0.037$		
Cancer staging			
T1	46 (71)	74 (79)	596 (76)
T2	19 (29)	20 (21)	184 (24)
P value	$P = 0.497$		
Cancer risk,[c] *n* (%)			
Low	31 (48)	64 (68)	432 (55)
Intermediate	31 (48)	29 (31)	332 (43)
High	2 (3)	1 (1)	15 (2)
P value	$P = 0.027$		
Biopsy cores invaded with cancer, *n* (%)			
1	20 (32)	33 (37)	250 (33)

(*Continued*)

Table 3. Continued

Baseline factor	Changed to a radical treatment[a] (n = 65)	Changed to active monitoring[b] (n = 94)	Received original preference (n = 780)
2	13 (20)	20 (22)	147 (19)
3+	31 (48)	36 (40)	369 (48)
P value	$P = 0.446$		
Perineural invasion			
No (%)	54 (83)	77 (86)	595 (78)
Yes (%)	11 (17)	13 (14)	163 (22)
P value	$P = 0.227$		
Length of tumors, (minimum *n*)	$n = 58$	$n = 83$	$n = 711$
Medium maximum length (mm) in any 1 core (IQR)	3.0 (1.0, 6.0)	2.0 (1.0, 5.0)	3.0 (1.0, 6.0)
P value	$P = 0.718$		
Median aggregate length (mm) of tumors (IQR)	5.0 (2.0, 17.0)	4.0 (1.5, 9.0)	4.0 (2.0, 12.0)
P value	$P = 0.238$		

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen.

P values are three-way comparisons, using a logistic or ordinal logistic model followed by a Wald test for categorical outcomes and a Kruskal–Wallis test for continuous outcomes.

[a] Moving from an initial preference of active monitoring to receiving radical prostatectomy, radiotherapy, or brachytherapy.

[b] Moving from an initial preference of radical prostatectomy, radiotherapy, or brachytherapy to receiving active monitoring.

[c] Risk was defined as "Low" if T1 and G $\leq$ 6 and pccPSA $<$ 10, "High" if G $\geq$ 8, and "Intermediate" for all other combinations of stage, grade, and PSA.

choice of treatment received, other than a suggestion that men who received surgery or radiotherapy had slightly worse urinary symptoms (Table A5).

4. Discussion

This analysis of all patients eligible for the ProtecT randomized trial of treatments for clinically localized prostate cancer has provided new insights into trial recruitment, particularly about treatment preferences and key decisions about participation and changes after randomization. Overall, the randomized and treatment choice groups in the ProtecT comprehensive cohort were very similar in relation to most baseline data except that those who chose a treatment were more likely to be in managerial/professional occupations and to have had a previous PSA test [17]. Among those who rejected randomization, more chose active monitoring than the other options, and these preferences were associated with low-risk disease. Preferences for radical treatments were associated with higher risk disease. A very similar percentage switched treatment from their random allocation (22%) as changed from an initially stated preference (20%). These changes were also associated with the same pattern of cancer risk features and occupation type. There was weaker evidence that men in managerial/professional occupations were more likely than those in other occupation groups to change from the random allocation, but stronger evidence they were more likely to change from their initial preference to another treatment and choose options only available outside the RCT, such as brachytherapy.

There were only a small number of examples where there was some evidence that factors captured by PROMs appeared to influence decision-making, for example, weak evidence that men with lower levels of anxiety and depression or some bowel and sexual symptoms were more likely to change to active monitoring and some with bothersome urinary symptoms to opt for a radical option. The groups defined according to treatments received also reflected the influences of selection by prostate cancer risk features and occupation type.

The ProtecT trial provided the opportunity to investigate the influences of baseline factors on RCT participation decisions because of its comprehensive cohort design and a recruitment intervention that included active discussion of treatment preferences [17,23,24]. In most RCTs, data are primarily (sometimes only) available for those who have agreed to be randomized, with little, if any, consideration of those not participating. In ProtecT, the treatment RCT was preceded by a program of population-based PSA testing, which included the collection of detailed baseline sociodemographic, clinical history, biopsy, and PROMs data on all men later diagnosed with localized prostate cancer and deemed eligible for the RCT (n = 2,664). A large proportion—1,643 men (62%)—agreed to be randomized between surgery, radiotherapy, and active monitoring, and the 997 who declined randomization had their treatment preference recorded and were followed up in the same way as the randomized. Other comprehensive cohort studies have tended to have small randomized cohorts [10] or were used to explore rarer outcomes [13] or generalizability [14]. To our knowledge, this is the first time that

Table 4. Baseline sociodemographic and clinical factors of those who accepted randomization, according to primary treatment received (regardless of randomized allocation) within 12 months

Baseline factor	Active monitoring ($n = 628$)	Surgery ($n = 488$)	Radiotherapy ($n = 470$)	Brachytherapy ($n = 21$)
Age (*n*)	*n* = 628	*n* = 488	*n* = 470	*n* = 21
Median age (IQR)	62.0 (58.0, 66.0)	61.0 (57.0, 65.0)	62.0 (58.0, 66.0)	59.0 (53.0, 62.0)
P value	$P = 0.005$			
Ethnicity				
White, *n* (%)	615 (99)	477 (98)	459 (99)	21 (100)
Other, *n* (%)	8 (1)	8 (2)	4 (1)	0 (0)
P value	$P = 0.567$			
Marital status, *n* (%)				
Married/living as married	511 (82)	416 (86)	405 (87)	16 (76)
Other (e.g., divorced)	114 (18)	67 (14)	62 (13)	5 (24)
P value	$P = 0.062$			
Occupation (present or last paid), *n* (%)				
Managerial	260 (42)	207 (43)	189 (41)	15 (71)
Intermediate	100 (16)	65 (13)	85 (18)	1 (5)
Working	261 (42)	210 (44)	187 (41)	5 (24)
P value	$P = 0.130$			
Cancer/treatment history, *n* (%)				
Previous PSA test	80 (13)	75 (16)	63 (14)	5 (25)
P value	$P = 0.333$			
Previous urinary/prostate treatment	61 (10)	45 (9)	32 (7)	3 (15)
P value	$P = 0.257$			
Family history of cancer (prostate only)	45 (8)	34 (8)	38 (9)	1 (5)
P value	$P = 0.837$			
Family history of cancer (all)	339 (58)	273 (59)	259 (59)	9 (45)
P value	$P = 0.636$			
Deprivation score, *n* (%)				
Living in an area of deprivation	95 (15)	78 (16)	62 (13)	1 (5)
P value	$P = 0.410$			
PSA level (minimum *n*)	*n* = 628	*n* = 488	*n* = 470	*n* = 21
Median baseline PSA level (IQR)	4.4 (3.6, 6.4)	4.7 (3.7, 6.9)	4.8 (3.7, 6.9)	4.3 (3.5, 5.7)
P value	$P = 0.041$			
Median biopsy PSA level (IQR)	4.5 (3.5, 6.6)	5.1 (3.7, 7.3)	4.9 (3.6, 7.4)	4.2 (3.3, 4.8)
P value	$P = 0.004$			
Gleason score, *n* (%)				
6	503 (80)	366 (75)	352 (75)	18 (86)
7	116 (18)	112 (23)	103 (22)	3 (14)
8–10	9 (1)	10 (2)	15 (3)	0 (0)
P value	$P = 0.074$			
Cancer staging, *n* (%)				
T1	491 (78)	361 (74)	351 (75)	19 (90)
T2	137 (22)	127 (26)	119 (25)	2 (10)
P value	$P = 0.147$			
Cancer risk[a]				
Low	382 (61)	271 (56)	265 (56)	14 (67)
Intermediate	237 (38)	207 (42)	190 (40)	7 (33)
High	9 (1)	10 (2)	15 (3)	0 (0)
P value	$P = 0.145$			

(*Continued*)

Table 4. Continued

Baseline factor	Active monitoring (n = 628)	Surgery (n = 488)	Radiotherapy (n = 470)	Brachytherapy (n = 21)
Biopsy cores invaded with cancer, *n* (%)				
1	203 (33)	152 (32)	141 (30)	6 (29)
2	136 (22)	91 (19)	94 (20)	7 (33)
3+	281 (45)	238 (49)	232 (50)	8 (38)
P value	$P = 0.530$			
Perineural invasion, *n* (%)				
No	503 (81)	376 (79)	365 (78)	18 (86)
Yes	115 (19)	101 (21)	101 (22)	3 (14)
P value	$P = 0.508$			
Length of tumors (minimum *n*)	$n = 569$	$n = 439$	$n = 428$	$n = 18$
Medium maximum length (mm) in any 1 core (IQR)	2.0 (1.0, 5.0)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)	2.5 (2.0, 4.0)
P value	$P = 0.229$			
Median aggregate length (mm) of tumors (IQR)	4.0 (2.0, 10.0)	5.0 (2.0, 12.0)	5.0 (2.0, 13.0)	4.0 (3.0, 10.0)
P value	$P = 0.184$			

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen.

P values are four-way comparisons, using a logistic or ordinal logistic model followed by a Wald test for categorical outcomes and a Kruskal–Wallis test for continuous outcomes.

[a] Risk was defined as "low" if T1 and G $\leq$ 6 and pccPSA $<$ 10, "high" if G $\geq$ 8, and "intermediate" for all other combinations of stage, grade, and PSA.

associations between baseline factors and RCT recruitment and participation decisions have been so comprehensively investigated.

Although many baseline socioeconomic, clinical history, biopsy findings, and PROMs data were collected, only cancer risk features were strongly and consistently associated with decision-making. However, there was weaker evidence that men in managerial/professional occupations were more likely to exercise choices at each stage of research participation than men in other occupational groups. They were more likely than those in other occupations to respond and agree to participate during the PSA testing and diagnostic program [17], more likely to reject randomization and choose their preferred treatment, and also to change their minds after their initially stated preference. They changed in both directions: to active monitoring from a radical option and from a radical option to active monitoring. They were also more likely to actively seek options outside usual practice—a PSA test before the ProtecT invitation [17]—or brachytherapy, not available in the RCT.

Previous research has identified employment status and level of education as factors associated with treatment preferences and participation in RCTs, although usually in relation to underparticipation of more deprived groups [25]. However, if the findings shown here are occurring in other RCTs, this may explain some fraction of the poor RCT recruitment seen more generally. This novel finding needs to be investigated in other RCTs. It suggests a potential need for targeted information for this group (those with managerial/professional occupations) so that they can better understand the rationale for RCTs and randomization.

Selection by prostate cancer risk features was also seen in the treatments received cohort. Observational studies also typically show that surgery and radiotherapy are received by men with higher risk disease and active surveillance by men with lower risk disease and also that lower income/education/occupation groups tend to receive radiotherapy [26–28]. Younger fitter men have tended to receive surgery, and older less fit men receive radiotherapy in observational studies, whereas in ProtecT, the treatment groups were very similar in age and fitness [16]. This and other unmeasured confounding might explain why the superiority of surgery over radiotherapy in terms of mortality and cancer outcomes seen in observational studies [26] was not seen in the ProtecT trial primary analysis at a median of 10 years [29].

Patients' treatment preferences are usually considered to make recruitment difficult [6,7] and increase switching [30]. Previous research in ProtecT, however, showed that when recruiters gently explored and addressed initially expressed preferences, the numbers of patients willing to consider randomization increased and numbers later switching were reduced [23,24,31]. Research suggesting that treatment preferences are often constructed during elicitation and are sensitive to contextual factors supports this approach [32].

Recruitment in ProtecT was guided by a complex intervention [24]. A high percentage of eligible patients agreed to be randomized (62%) compared with around 20% in a similar RCT [33]. The randomized and treatment choice cohorts had very similar baseline data, there were consistent and plausible factors associated with treatment

Table 5. Baseline sociodemographic and clinical factors of those who declined randomization and chose their treatment, according to primary treatment received within 12 mo

Baseline factor	Active monitoring ($n = 507$)	Surgery ($n = 262$)	Radiotherapy ($n = 133$)	Brachytherapy ($n = 56$)
Age (*n*)	*n* = 507	*n* = 262	*n* = 133	*n* = 56
Median age (IQR)	62.0 (58.0, 65.0)	62.0 (58.0, 65.0)	62.0 (58.0, 65.0)	60.5 (56.0, 64.0)
P value	$P = 0.004$			
Ethnicity, *n* (%)				
White	500 (99)	259 (100)	131 (99)	56 (100)
Other	6 (1)	1 (0)	1 (1)	0 (0)
P value	$P = 0.557$			
Marital status, *n* (%)				
Married/living as married	419 (83)	231 (89)	108 (82)	50 (89)
Other (e.g., divorced)	87 (17)	29 (11)	23 (18)	6 (11)
P value	$P = 0.102$			
Occupation (present or last paid), *n* (%)				
Managerial	256 (52)	142 (55)	48 (36)	43 (80)
Intermediate	82 (17)	38 (15)	24 (18)	7 (13)
Working	158 (32)	79 (31)	60 (45)	4 (7)
P value	$P < 0.001$			
Cancer/treatment history, *n* (%)				
Previous PSA test	76 (15)	58 (22)	17 (13)	16 (29)
P value	$P = 0.007$			
Previous urinary/prostate treatment	33 (7)	25 (10)	15 (11)	5 (9)
P value	$P = 0.232$			
Family history of cancer (prostate only)	42 (9)	25 (11)	9 (8)	5 (10)
P value	$P = 0.876$			
Family history of cancer (all)	277 (58)	151 (61)	68 (56)	29 (55)
P value	$P = 0.731$			
Deprivation score, *n* (%)				
Living in an area of deprivation	60 (12)	32 (12)	11 (9)	4 (7)
P value	$P = 0.511$			
PSA level (minimum *n*)	*n* = 461	*n* = 233	*n* = 110	*n* = 41
Median baseline PSA level (IQR)	4.6 (3.5, 6.5)	4.9 (3.7, 6.8)	5.4 (4.0, 8.0)	4.3 (3.5, 5.9)
P value	$P = 0.002$			
Median biopsy PSA level (IQR)	4.7 (3.6, 6.7)	4.9 (3.7, 7.5)	5.1 (3.9, 7.5)	4.2 (3.4, 6.4)
P value	$P = 0.064$			
Gleason score, *n* (%)				
6	417 (82)	184 (71)	87 (65)	36 (63)
7	88 (17)	67 (26)	39 (29)	20 (35)
8–10	2 (<1)	9 (3)	7 (5)	1 (2)
P value	$P < 0.001$			
Cancer staging, *n* (%)				
T1	399 (79)	191 (73)	95 (71)	44 (79)
T2	108 (21)	71 (27)	38 (29)	12 (21)
P value	$P = 0.164$			
Cancer risk[a]				
Low	321 (63)	138 (53)	52 (39)	26 (46)
Intermediate	184 (36)	113 (43)	74 (56)	30 (54)
High	2 (<1)	9 (3)	7 (5)	0 (0)
P value	$P < 0.001$			

(*Continued*)

Table 5. Continued

Baseline factor	Active monitoring (n = 507)	Surgery (n = 262)	Radiotherapy (n = 133)	Brachytherapy (n = 56)
Biopsy cores invaded with cancer, *n* (%)				
1	198 (40)	69 (27)	30 (23)	12 (21)
2	97 (20)	44 (17)	27 (20)	16 (29)
3+	201 (41)	140 (55)	76 (57)	28 (50)
P value	$P < 0.001$			
Perineural invasion, *n* (%)				
No	414 (84)	191 (75)	92 (69)	41 (31)
Yes	9 (16)	62 (25)	41 (31)	41 (31)
P value	$P = 0.001$			
Length of tumors (minimum *n*)	$n = 471$	$n = 223$	$n = 125$	$n = 50$
Medium maximum length (mm) in any 1 core (IQR)	2.0 (1.0, 5.0)	3.0 (1.0, 6.0)	4.0 (2.0, 7.0)	3.0 (1.0, 6.0)
P value	$P < 0.001$			
Median aggregate length (mm) of tumors (IQR)	3.0 (1.0, 8.5)	5.0 (2.0, 13.0)	6.0 (2.3, 15.8)	4.0 (2.0, 12.0)
P value	$P < 0.001$			

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen.

P values are four-way comparisons, using a logistic or ordinal logistic model followed by a Wald test for categorical outcomes and a Kruskal Wallis test for continuous outcomes.

[a] Risk was defined as "low" if T1 and G $\leq$ 6 and pccPSA $<$ 10, "high" if G $\geq$ 8 and "intermediate" for all other combinations of stage, grade, and PSA.

preferences and switching/changing, and a similar percentage changed from the allocation as from an initial preference. The consistency of the findings in relation to risk categorization and occupation type permits some speculation about preferences in the treatment choice cohort. It may have been that men in managerial/professional occupations enquired about the details of their biopsy findings and used these to form their preferences. It is also possible that once patients declined randomization, their appointments became more like usual clinical practice, with clinicians using biopsy findings and risk categorization alongside a patient's preferences to reach "clinically appropriate" shared decisions [3]. The "clinical influence" might also account for surgery being chosen much more frequently as a radical option than radiotherapy (lead investigators were mostly surgeons), and the majority of men with small volume low-risk disease gravitating toward active monitoring. A combination of these factors is probably most likely. In other RCTs, patients' preferences have also been observed to be accepted quickly if they accord with clinicians' views [5,31,34]. These findings suggest that interventions to support clinicians with equipoise and exploring patient preferences could improve RCT recruitment more widely. However, these speculations require further investigation.

The strengths of this study relate to the use of a comprehensive cohort RCT design, recruitment intervention, and wide range of available data enabling detailed investigation of RCT participation decisions. Limitations include that the study was embedded in one RCT, and therefore, the particular features of ProtecT, including the disease area and high randomization rate, may not have relevance for other RCTs. In addition, associations with many data items were tested; positive findings require replication or further investigation in other RCTs.

In terms of future research, this article has identified opportunities to improve recruitment. The comprehensive cohort design could be used more often for this purpose, although its resource requirements may limit it to major questions of public health importance or controversy. More research is needed to better understand the effects of patient preferences and equipoise on RCT recruitment, potentially including further developing the recruitment intervention initiated in ProtecT to support recruiters with these challenges [35]. More research is also needed to investigate whether those in professional/managerial occupations are also rejecting randomization more often in other RCTs and need different information.

5. Conclusion

The treatment choice and treatment-received cohorts in the ProtecT study reflected prostate cancer disease selection factors: active monitoring being associated with lower risk disease and surgery/radiotherapy with intermediate- and high-risk diseases. There were few examples where other factors, including those captured by PROMs, influenced decision-making. As cancer risk features reflect biopsy findings, there may have been an interplay between men in managerial/professional occupations using these details to exercise their preferences, and clinicians steering patients toward clinically appropriate choices. These findings

also suggest a renewed role for comprehensive cohort studies and provide new insights to enable the development or extension of interventions to support recruiters with issues of equipoise and preferences to improve RCT recruitment.

CRediT authorship contribution statement

Jenny L. Donovan: Conceptualization, Funding acquisition, Writing - original draft, Writing - review & editing. **Brent Opmeer:** Formal analysis, Writing - review & editing, Writing - original draft. **Grace J. Young:** Formal analysis, Writing - review & editing, Writing - original draft. **Nicola Mills:** Methodology, Writing - review & editing. **Richard M. Martin:** Methodology, Writing - review & editing. **J. Athene Lane:** Methodology, Writing - review & editing. **Chris Metcalfe:** Methodology, Writing - review & editing. **Tim J. Peters:** Methodology, Writing - review & editing. **Michael Davis:** Methodology, Writing - review & editing. **Emma L. Turner:** Methodology, Writing - review & editing. **Eleanor Walsh:** Methodology, Writing - review & editing. **David E. Neal:** Funding acquisition, Writing - review & editing. **Freddie C. Hamdy:** Funding acquisition, Writing - review & editing. **Peter Holding:** Investigation, Writing - review & editing. **Malcolm Mason:** Investigation, Writing - review & editing. **James W.F. Catto:** Investigation, Writing - review & editing. **Derek J. Rosario:** Investigation, Writing - review & editing. **John Staffurth:** Investigation, Writing - review & editing. **Howard Kynaston:** Investigation, Writing - review & editing. **Owen Hughes:** Investigation, Writing - review & editing. **Prasad Bollina:** Investigation, Writing - review & editing. **Alan Doherty:** Investigation, Writing - review & editing. **Vincent Gnanapragasam:** Investigation, Writing - review & editing. **Roger Kockelbergh:** Investigation, Writing - review & editing. **Alan Paul:** Investigation, Writing - review & editing. **Edgar Paez:** Investigation, Writing - review & editing. **David Gillatt:** Investigation, Writing - review & editing. **Edward Rowe:** Investigation, Writing - review & editing. **Jon Oxley:** Investigation, Writing - review & editing.

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Supplementary data

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